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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
KAM, CHIH MIN	
ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 12/24/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/869,916	KOHNO ET AL.	
	Examiner	Art Unit	
	Chih-Min Kam	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 September 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *10-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6/4/03* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of the Claims

1. Claims 10-16 are pending.

Applicants' amendment filed on September 11, 2003 is acknowledged. Applicants' response has been fully considered. Claims 1-9 have been cancelled, and claims 10-16 have been added. Thus, claims 10-16 are examined.

Rejection Withdrawn

Claim Rejections - 35 USC § 101

2. The previous objection of claim 8 under 35 U.S.C. 101, regarding the claimed recitation of a use, without setting forth any steps involved in the process, is withdrawn in view of applicant's cancellation of the claim in the amendment filed September 11, 2003.

Claim Rejections - 35 USC § 112

3. The previous rejection of claims 1-9 under 35 U.S.C.112, first paragraph, is withdrawn in view of applicant's cancellation of the claim in the amendment filed September 11, 2003.

4. The previous rejection of claims 1-9 under 35 U.S.C.112, second paragraph, is withdrawn in view of applicant's cancellation of the claim in the amendment filed September 11, 2003.

Claim Rejections - 35 USC § 102

5. The previous rejection of claims 1-9 under 35 U.S.C. 102(e) as being anticipated by Dent *et al.* (U.S. Patent 6,147,107), is withdrawn in view of applicant's cancellation of the claim in the amendment filed September 11, 2003.

Claim Objections

6. Claim 11 is objected to because of the use of "A combination as claimed in claim 10". Since claim 11 is dependent from claim 10, use of "The combination as claimed in claim 10" is suggested.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 10, 11 and 13-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a combination of TZT-1027 and PD98059 as a MAP kinase inhibitor for treating tumor, a method of treating tumor in vitro or a method of potentiating the antitumor effect of TZT-1027 using the combination, and a pharmaceutical product comprising the combination; or, a method of enhancing the killing of cancer cells comprising administering a combination of TZT-1027 and a p42/44 MAP kinase cascade inhibitor such as PD98059 as indicated in the prior art, does not reasonably provide enablement for a combination of TZT-1027 and an ERK-MAP kinase inhibitor for treating tumor; an agent for potentiating the antitumor effect of TZT-1027 which contains an ERK-MAP kinase inhibitor; a method of treating tumor or a method for potentiating the antitumor effect of TZT-1027 by administering the combination; or a pharmaceutical product comprising the combination, where the structure of ERK-MAP kinase inhibitor is not defined. The specification does not enable a person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 10, 11 and 13-16 encompass a combination of TZT-1027 and an ERK-MAP kinase inhibitor for treating tumor (claims 10 and 11); an agent for potentiating the antitumor effect of TZT-1027 which contains an ERK-MAP kinase inhibitor (claim 13); a method of treating tumor or potentiating the antitumor effect of TZT-1027 using the combination (claims 14 and 15), and a pharmaceutical product comprising the combination (claim 16). The specification, however, only discloses cursory conclusions without data supporting the findings, which state that when a microtubule-interfering agent such as TZT-1027 having an antitumor effect is used in combination with an ERK-MAP kinase cascade inhibitor, the antitumor activity of microtubule-interfering agent is remarkably potentiated (page 3, lines 23-28). There are no indicia that the present application enables the full scope in view of the use of a combination of TZT-1027 and an ERK-MAP kinase inhibitor for treating tumor as discussed in the stated rejection. The present application provides no indicia and no teaching/guidance as to how the full scope of the claims is enabled. The factors considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F2d at 731,737, 8 USPQ2d at 1400,1404 (Fed. Cir.1988)). The factors most relevant to this rejection are the breath of the claims, the absence of working examples, the state of the prior art and relative skill of those in the art, the unpredictability of the art, the nature of the art, the amount of direction or guidance presented, and the amount of experimentation necessary.

(1). The breath of the claims:

The breath of the claims is broad and encompasses unspecified variants regarding the identities of the ERK-MAP kinase inhibitors used in the combination, and the in vivo treating

conditions using the combination, which are not adequately described or demonstrated in the specification.

(2). The presence or absence of working examples:

There are no working examples indicating the claimed methods in association with the variants except for the use of a combination of TZT-1027 or vincristine with PD98059 in treating tumor cells in vitro (Example, pages 9-13).

(3). The state of the prior art and relative skill of those in the art:

The prior art (e.g., the combined references of Dent *et al.*, U.S. Patent 6,147,107and Kobayashi *et al.*, Jpn. J. Cancer Res. 88, 316-327, 1997) teaches the use of a p42/44 MAP kinase cascade inhibitor such as PD98059 in combination with TZT-1027 in treating tumor cells, where the administration of the inhibitor will potentiate the ability of chemotherapy of the antitumor agent. However, the general knowledge and level of the skill in the art do not supplement the omitted description, the specification needs to provide specific guidance on the identities of various ERK-MAP kinase inhibitor used in the combination, and the in vivo treating conditions using the combination to be considered enabling for variants.

(4). Predictability or unpredictability of the art:

The claims encompass the use of a combination of TZT-1027 and an ERK-MAP kinase inhibitor for treating tumor. However, the identities of various ERK-MAP kinase inhibitors used in the combination, and the in vivo treating conditions using the combination are not sufficiently described in the specification, thus, the effect of the combination is not predictable.

(5). The amount of direction or guidance presented and the quantity of experimentation necessary:

The claims are directed to the use of a combination of TZT-1027 and an ERK-MAP kinase inhibitor for treating tumor. The specification has indicated the use of a combination of TZT-1027 or vincristine with PD98059 in treating tumor cells in vitro, where PD98059 potentiates the antitumor activity TZT-1027 or vincristine (Example, pages 9-13), and a general dosage for a microtubule-interfering agent and an ERK-MAP kinase inhibitor in the treatment (page 9, lines 10-19). However, the specification fails to demonstrate the use of TZT-1027 and various ERK-MAP kinase inhibitors in the combination for treatment of tumor in vivo. For example, the specification has not shown the treating conditions such as dosage, the time for in vivo treatment using TZT-1027 and a specific ERK-MAP kinase inhibitor in the combination treatment, nor has demonstrated the effect of the combination in the treatment of tumor. Furthermore, the specification has not shown how to extrapolate the in vitro results to in vivo effect. There are no working examples indicating the claimed methods using the combination. Since the specification fails to provide sufficient guidance on the identities of various ERK-MAP kinase inhibitors used in the combination and the in vivo treating conditions, it is necessary to have additional guidance and to carry out further experimentation to assess the effects of potentiating TZT-1027 for various ERK-MAP kinase inhibitors in the combination therapy.

(6). Nature of the Invention

The scope of the claims includes the use of a combination of TZT-1027 and an ERK-MAP kinase inhibitor for treating tumor, but the specification has not demonstrated the use of various ERK-MAP kinase inhibitors with TZT-1027 in the combination, and the in vivo treating conditions using the combination. Thus, the disclosure is not enabling for the reasons discussed above.

In summary, the scope of the claim is broad, while the working example does not demonstrate the claimed variants and methods, and the teachings in the specification are limited, therefore, it is necessary to have additional guidance and to carry out further experimentation to assess the effects of the combination of TZT-1027 and various ERK-MAP kinase inhibitors in the treatment of tumors.

In response, applicants indicate the new claims have been limited to a specific microtubule-interfering agent, TZT-1027, which has a weaker neurotoxicity than that of existing medicines such as vincristine and paclitaxel as indicated in the provided reference (Ogawa et al., 2001; Exhibit A); TZT-1027 has microtubule-interfering activity 100 to 1000 times as strong as that of vincristine as indicated by inventors' own publication; regarding the ERK-MAP kinase inhibitors, the specification has fully described these inhibitors to the extent, one skilled in the art can practice the claimed invention; MAP kinase cascade has been studied extensively, e.g., Dent reference, and it is well known blocking any part of the cascade results in an inhibition of entrance of the effector molecule p90 ribosomal S6 kinase into the nucleus of the cell; and the crucial point of the present invention resides in that this inhibitory action potentiates the antitumor activity of TZT-1027, thus, one skilled in the art would reasonably expect any compound having such inhibitory action, regardless of species, would potentiate the antitumor activity of TZT-1027 (pages 5-8 of the response). The response has been fully considered, however, the argument is not found persuasive because the claims encompass a combination of TZT-1027 with various ERK-MAP kinase inhibitors having different structures, however, the effects of these different inhibitors to potentiate the antitumor activity of TZT-1027 in the combination, and the effects of the combination of TZT-1027 and various ERK-MAP kinase

inhibitors in the treatment of tumors have not been demonstrated in the specification. For example, the specification demonstrates PD-98059 potentiates the antitumor activity of TZT-1027 in vitro, however, the specification has not shown an inhibitor with different structure has the same potentiating effect, nor has demonstrated how to extrapolate the effect of PD-98059 to a different inhibitor (e.g., PD184352 in Dent patent). As indicated in the section above, the specification has not provided sufficient teachings regarding the claimed method, thus it is necessary to carry out further experimentation to assess the effects of various ERK-MAP kinase inhibitors in potentiating the antitumor activity of TZT-1027, and the effect of the combination in treating tumors.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 14-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

9. Claims 14-15 are indefinite because the claim lacks essential steps in the method of treatment of a tumor or the method of potentiating the antitumor effect. The omitted step(s) are: the outcome of the treatment for claim 14; and the effective amounts of TZT-1027 and an ERK-MAP kinase cascade inhibitor, and the outcome of the process for claim 15.

In response, applicants indicate the new claim 14 recites therapeutically effective amount of TZT-1027 and an ERK-MAP kinase inhibitor, and claim 15 is drafted in method of use form. The response has been fully considered, however, the argument is not found persuasive because

both claims do not recite the outcome of the process, and claim 15 also lacks the effective amount of agent used.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

10. Claim 12 is rejected under 35 U.S.C. 102(b) as being anticipated by Kobayashi *et al.* (Jpn. J. Cancer Res. 88, 316-327, March 1997).

Kobayashi *et al.* teach TZT-1027 exhibits antitumor activity when administered to mice having a variety of transplantable tumors (Table 1; pages 319-320; claim 12). The term "for use in combination with an ERK-MAP kinase cascade inhibitor" is an intended use, which does not play weight in the patentability of the claimed agent, thus, the agent containing TZT-1027 meets the criteria of claim 12.

11. Claim 13 is rejected under 35 U.S.C. 102(e) as being anticipated by Dent *et al.* (U.S. Patent 6,147,107, filed on December 20, 1998).

Dent *et al.* teach the administration of a p42/44 MAP kinase cascade inhibitor such as PD98059 in combination with a lethal agent such as vincristine in a method of killing cancer cells, and the MAP kinase inhibitor may be administered either in combination with or separately from the chemotherapeutic agent (column 4, lines 7-33; column 7, line 62-column 8, line 9; claim 13). The term "for potentiating the antitumor effect of TZT-1027" is an intended use, which does not play weight in the patentability of the claimed agent, thus, the agent containing a p42/44 MAP kinase cascade inhibitor meets the criteria of claim 13.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

12. Claim 10-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dent *et al.* (U.S. Patent 6,147,107) in view of Kobayashi *et al.* (Jpn. J. Cancer Res. 88, 316-327, March 1997).

Dent *et al.* teach a method of killing cancer cells comprising administering a p42/44 MAP kinase cascade inhibitor such as PD98059 in combination with an antitumor agent such as vincristine, and the MAP kinase inhibitor may be administered either in combination with or separately from the chemotherapeutic agent (column 4, lines 7-33; column 7, line 62-column 8, line 9; claims 10, 11). The administration of such inhibitor will potentiate the ability of chemotherapy of the lethal agents to cause apoptosis of cancer cells, thus decreasing cancer recurrences (column 4, lines 34-37; claims 13 and 15). The p42/44 MAP kinase cascade inhibitor, PD98059 is an ERK-MAP kinase cascade inhibitor, which is cited in the specification (page 7, lines 3-5). Where Dent *et al.* disclose the combination of antitumor agent and ERK-MAP kinase cascade inhibitor PD98059, it is administered as a composition which is a pharmaceutical (see e.g., column 8, line 42+ to column 9, line 21), and the patent at columns 7 to 8 discuss the combined use, which meet the criteria of claim 16 reciting packaging/instructions regarding use of the compounds in combination. However, Dent *et al.* do not disclose the use of TZT-1027. Kobayashi *et al.* teach TZT-1027 exhibits antitumor activity when administered to mice having a variety of transplantable tumors, and the antitumor activity of TZT-1027 against these tumors are superior than vincristine (Table 1; pages 319-320; claim 12). At the time of invention was made, it would have been obvious to one of ordinary skill in the art to use TZT-1027 as taught by Kobayashi *et al.* in combination with an ERK-MAP kinase cascade inhibitor in the method of treating tumors as taught by Dent *et al.* (claim 14) because one of ordinary skill in

the art would have been motivated to use a superior antitumor agent in combination of an ERK-MAP kinase cascade inhibitor for effective treatment of tumors. Thus, the combined references result in the claimed invention and was, as a whole, prima facie obvious at the time the claimed invention was made.

Conclusion

13. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (703) 308-9437. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (703) 308-2923. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-0294 for regular communications and (703) 308-4227 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Chih-Min Kam, Ph. D. CMK
Patent Examiner

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December 16, 2003

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